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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/364,847	07/30/1999	OLIVER P. PEOPLES	MBX030	9982

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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/364,847	PEOPLES ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Application Status

Claims 1-6 are pending in the application.

Applicants' amendment to claims 1 and 6 in Paper No. 25, filed 01/02/03, is acknowledged.

Applicants' arguments presented in Paper No. 25 have been fully considered and are deemed to be persuasive to overcome the objections previously applied.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, First Paragraph

1. The written description rejection of claims 1-6 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 2 of Paper No. 24).

Applicants traverse (beginning at page 9 of Paper No. 25) the instant rejection by citing case law. Applicants argue (beginning at page 11 of Paper No. 25) the specification has disclosed more than enough sequences encoding enzymes of the fusion to practice the claimed method and argue that the written description requirement of 35 USC 112, first paragraph, should be applied to the claimed subject matter. Applicants argue the rejection has been made as if applicants were claiming the genes. Applicants argue the disclosure of six representative species of claimed fusion proteins is sufficient to meet the written description requirement. Applicants argue the identifying characteristic for each claimed fusion protein lies within the nucleic acid encoding each fusion protein and many examples of genes encoding enzymes of the PHA biosynthetic pathway have been disclosed in the specification. Applicants argue that the examiner's assertion that the specification fails to describe other representative examples of fusion proteins "is absurb" as the enzymes comprising the fusion are defined by function and the structure is defined by the nucleic acid encoding each enzyme of the fusion. Applicants' arguments are not found persuasive.

It is noted that the instant claims are not drawn to a method as asserted by applicants (see line 2 of page 11 of Paper No. 25) and are instead drawn to a product, i.e., a fusion of two enzymes (see line 1 of claim 1 as amended in Paper No. 25). The examiner acknowledges applicants' argument that the name of an enzyme indicates its function and further acknowledges the disclosure at pages 8-11 of the instant specification of references describing genes encoding individual enzymes of the claimed two-enzyme fusion. Further, the examiner agrees with applicants' argument to the extent that the species of beta-ketothiolase-, acyl-coA reductase-, PHA synthase-, PHB synthase-, phasing-, enoyl-CoA hydratase-, and beta-hydroxyacyl-ACP::coenzyme-A transferase-encoding nucleic acids from specifically cited sources have been disclosed in the specification at pages 8-11. However, this disclosure fails to describe the claimed invention in such a way that a skilled artisan would recognize that applicants were in possession of all species of beta-ketothiolase-, acyl-coA reductase-, PHA synthase-, PHB synthase-, phasing-, enoyl-CoA hydratase-, and beta-hydroxyacyl-ACP::coenzyme-A transferase-encoding nucleic acids from *any* source. The specification fails to adequately describe all species of the genus of recited beta-ketothiolases from all sources, all species of the genus of recited acyl-CoA reductases from all sources, all species of the genus of recited PHA synthases from all sources, all species of the genus of recited PHB synthases from all sources, all species of the genus of recited phasins from all sources, all species of the genus of recited enoyl-CoA hydratases from all sources, and all species of the genus of recited beta-hydroxyacyl-ACP::coenzyme-A transferases from all sources in such as a way that a skilled artisan would recognize that applicants were in possession of the claimed invention. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly with the enzymes of the two-enzyme fusion, the

functional definition of the genus does not provide structural information commonly possessed by all members of the genus, which distinguish the enzyme-encoding species within the genus such that a skilled artisan can visualize or recognize the identity of all species of recited enzymes from *any* source. The specification provides no disclosure of the structures of beta-ketothiolase-, acyl-coA reductase-, PHA synthase-, PHB synthase-, phasin-, enoyl-CoA hydratase-, and beta-hydroxyacyl-ACP::coenzyme-A transferase-encoding nucleic acid sequences besides those as disclosed from specific sources at pages 8-11 of the instant specification. Applicants state, "the degree of homology is such that the known and available genes can be used to isolate additional genes from other sources encoding the enzymes" (page 4, lines 7-9 of Paper No. 25). While the sequences of nucleic acids encoding beta-ketothiolases, acyl-coA reductases, PHA synthases, PHB synthases, phasins, enoyl-CoA hydratases, and beta-hydroxyacyl-ACP::coenzyme-A transferases as disclosed in the specification at pages 8-11 were known in the art at the time of the invention, one of skill in the art would recognize that based on the disclosure of these sequences there was, and still is, no way to predict or divine the enzyme-encoding sequences from sources other than those cited in the specification. For inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, more evidence is required to show possession. Based on the disclosed representative species, a skilled artisan would not be able to visualize or recognize the identity of all members of the claimed genus. Thus, given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

2. The scope of enablement rejection of claims 1-6 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 3 of Paper No. 24).

Applicants traverse (beginning at page 2 of Paper No. 25) the instant rejection by citing case law. Applicants argue (beginning at page 3 of Paper No. 25) the enzymes comprising the two-enzyme fusion are known and well-characterized, reagents and methods required for their expression are disclosed in

the specification, and actual working examples have been provided in the specification. Applicants argue the enzymes are limited to a very specific group of enzymes of the PHA biosynthesis pathway and such fusions are easily assayed. Applicants argue Medline indicates the amino acid and encoding nucleic acid sequences of these enzymes are known from multiple sources, the function is generally the same between enzymes of different sources, and the degree of homology between the known enzymes would enable one to isolate additional genes from other sources. Applicants argue there is no legal requirement that the specification enable all possible members encompassed by the claims and assert that the specification is required only to enable sufficient species to demonstrate they are entitled to the genus. Applicants cite pages 8-10 of the instant specification. Applicants argue the specification provides enablement for the entire scope of claimed fusion enzymes and if additional genes that are not disclosed in the specification are desired, these can be isolated and used to produce the claimed fusion enzymes. Applicants' arguments are not found persuasive.

Undue experimentation would be required for a skilled artisan to make the entire scope of claimed fusion enzymes. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). The specification provides only four working examples of the claimed fusion proteins: 1) a beta-ketothiolase-acyl CoA reductase (phbA-phbB) fusion enzyme from the fusion of *A. eutrophus* phbA and phbB genes as disclosed in the Example 1 at pages 18-23 of the instant specification, 2) a PHA synthase-beta-hydroxyacyl-ACP::coenzyme-A transferase (phaC-phbG) fusion enzyme from the fusion of *P. oleovorans* phaC and *P. putida* phbG genes as disclosed in the Example 3 at pages 24-26 of the instant specification, 3) a PHA synthase-enoyl-CoA hydratase (phaC-phaJ) fusion enzyme from the fusion of *Z. ramigera* phaC and *A. caviae* phaJ genes as disclosed in the Example 4 at pages 26-27 of the instant specification, and 4) a beta-ketothiolase-acyl CoA reductase (phbA-phbB)

fusion enzyme from the fusion of *R. eutropha* bktB and phaB genes as disclosed in the Example 5 at pages 28-29 of the instant specification. Applicants assert that the nucleic acid sequences of known PHA biosynthesis genes encoding the enzymes of claim 1, coupled with the four working examples as disclosed in the specification is sufficient to fully enable the entire scope of claimed fusion enzymes. However, this is not the case. While the examiner acknowledges that the specification and prior art fully enable the fusion enzymes as exemplified as Examples 1-5 of the instant specification, the specification does not reasonably provide enablement for a fusion protein of the formula E1-Ln-E2, wherein E1 and E2 catalyze successive reactions in a PHA pathway and are selected from the group consisting of: *all* beta-ketothiolases from any source, *all* acyl-CoA reductases from any source, *all* PHA synthases from any source, *all* PHB synthases from any source, *all* phasins from any source, *all* enoyl-CoA hydratases from any source, and *all* beta-hydroxyacyl-ACP::coenzyme-A transferases from any source or wherein E1 and E2 are selected from *any* phaA and phaB from any source; *any* phaB and phaA from any source; *any* phaC and phaP from any source; *any* phaP and phaC from any source; *any* phaC and phaG from any source; *any* phaG and phaC from any source; *any* phaC and phaJ from any source; and *any* phaJ and phaC from any source. The amount of direction and guidance provided by the prior art and the instant specification is insufficient to enable a skilled artisan to make the entire scope of claimed fusion enzymes. The examiner acknowledges the disclosure of PHA biosynthetic genes of pages 8-11 of the instant specification and the existence of methods for isolating other genes based on sequence identity to genes with known sequence. However, these methods, e.g., PCR and hybridization, require significant structural homology between the known sequence and the unknown sequence for their successful application and it is highly unpredictable as to whether all genes encoding the recited enzymes as broadly encompassed by the claims can be isolated based on sequence homology. Neither the prior art nor the specification provides a disclosure of the sequences of all nucleic acids encoding the enzymes as recited in claim 1. A skilled artisan would recognize that isolating the entire scope of nucleic acids encoding the entire scope of recited enzymes would constitute an undue amount of experimentation as there is no guidance provided in the specification as to a structural region or regions of a known gene of a PHA biosynthetic

pathway as recited in claim 1 that can predictably be used to isolate other unknown PHA biosynthetic genes from any source.

Also, as stated in a previous Office action, the peptide linker of claim 1 (claims 2 and 4-6) has any number of amino acids and the peptide linker of claim 3 has from zero to fifty amino acids. Applicants have provided guidance and working examples of the fusion proteins of SEQ ID NOs:10, 19, 33, 35, 49, and 51, having only two amino acids linking the two individual enzyme sequences. The prior art teaches that linkers from two to ten amino acids are optimal and that longer linkers are often prone to proteolytic degradation (page 230 of Bulow et al. Trends Biotechnol 9:226-231). Therefore, there is a high degree of unpredictability in making the claimed fusion proteins with a linker of any number of amino acids or greater than 10 amino acids in length.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

3. The rejection of claims 1-3, 5, and 6 under 35 U.S.C. 103(a) as being unpatentable over Peoples et al. (US Patent 5,245,023; hereafter referred to as "Peoples") in view of Bulow et al. (Trends Biotechnol 9:226-231; hereafter referred to as "Bulow") is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 6 of Paper No. 24).

Addressing the reference of Peoples, applicants argue (beginning at page 12 of Paper No. 25) the reference of Peoples teaches a fusion enzyme of PHA synthase and PHB synthase, enzymes which applicants assert do not catalyze successive reactions in the PHA biosynthesis pathway, but catalyze the same reaction using different substrates. Applicants argue the claimed method requires that the enzymes

of the two-enzyme fusion catalyze successive reactions. Applicants argue one of ordinary skill in the art could not predict the success of a fusion enzyme with individual enzymes catalyzing successive reactions based on the fusion as taught by Peoples for catalyzing the same reaction using different substrates. Addressing the reference of Bulow, applicants argue Bulow does not teach the use of fusion enzymes for increased production of PHB. Applicants' arguments are not found persuasive.

It is noted that the instant claims are drawn to a product and not a method as asserted by applicants at page 13, line 1 of Paper No. 25. Addressing applicants' argument regarding the reference of Peoples not teaching a fusion enzyme catalyzing successive reactions of the PHA biosynthesis pathway, the examiners agrees with applicants' argument – the examiner can find no teaching in the reference of Peoples specifically disclosing a fusion enzyme with enzymes catalyzing successive reactions. Addressing applicants' argument that Bulow does not teach the use of fusion enzymes for increased production of PHB, this appears to have been an editing error. Instead, it is the reference of Peoples that teaches the use of fusion enzymes for increased production of PHB. Addressing applicants' argument that the fusion enzyme of Peoples does not provide an indication of the success of a fusion enzyme of enzymes catalyzing successive PHA biosynthetic reactions, while the reference of Peoples alone *may* not indicate a reasonable expectation of success, it is the combination of Peoples and Bulow that provides a reasonable expectation of success to one of ordinary skill in the art for making the claimed fusion as follows:

- Peoples demonstrates the construction of fusion enzymes of the PHA biosynthetic pathway and shows that such enzymes were known in the art (column 23);
- Peoples teaches the isolation and primary sequences of *Zoogloea ramigera* and *Alcaligines eutrophus* native beta-ketothiolase, acetylacetyl-CoA reductase, and PHB polymerase genes (columns 6-14);
- Peoples teaches co-expression of the beta-ketothiolase, acetylacetyl-CoA reductase, and PHB polymerase genes in *Escherichia coli* results in the formation of PHB (columns 17-19);

- Bulow teaches that "If the entire primary sequences of the native enzymes are maintained in the fusion enzymes, the enzymes usually retain most of their native specific activities despite being fused together" (page 230, left column, top); and
- Bulow discloses many advantages of fusing enzymes, in particular for catalyzing successive enzymatic reactions (page 231).

Neither Applicants nor the references of Peoples and Bulow provide any evidence that an ordinarily skilled artisan would not have motivation or a reasonable expectation of success for making the claimed invention. Therefore, the cited references teach all claim limitations and a motivation and reasonable expectation of success for making the claimed fusion and thus the cited references render obvious the claimed invention.

4. The rejection of claim 4 under 35 U.S.C. 103(a) as being unpatentable over Peoples in view of Bulow as applied to claims 1-3, 5, and 6 above, and further in view of Argos (J Mol Biol 211:943-958, 1990) is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 6 of Paper No. 24).

The examiner can find no response to the instant rejection in the response of Paper No. 25. Thus, in the absence of a response, the rejection is maintained for the reasons of record.

Conclusion

5. All claims are rejected. No claim is in condition for allowance.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally

be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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Patent Examiner
Art Unit 1652

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